ALBINISM AND HETEROCHROMIA IRIDES IN THE HEREFORD

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INTRODUCTION

Although albinism in cattle has been reported on a number of occasions (4, 8, 11, 18, 22, 24, 30, 35, 39, 46, 57), there are many anatomic, physiologic and genetic aspects that are not understood. Investigations of albino animals in two herds located in different areas of Kansas are presented in this thesis.

The first herd consisted of 90 beef animals of which 60 were albinos. Since 1951, when the first albino, a Hereford heifer purchased in dam, was born, the owner has attempted to develop a new breed of white beef cattle. The history of this herd is important because it suggests that this type of albinism is a dominant trait rather than the usual recessive.

Additional information is provided by findings in another herd containing albino animals. In 1962, a single albino heifer was examined in a southwestern Kansas Hereford herd. Recent re-examination revealed that this herd contained two albinos, the heifer, now a cow, and her son, and 25 normal colored Hereford cows exhibiting binocular pigment anomalies. The results of clinical, genetic, and histologic investigations of this herd are reported here, which together with those from the other albino herd, present evidence of irregularities and complexities in the expression and inheritance of albinism not previously noted in cattle.

REVIEW OF LITERATURE

The normal color of the skin and the cutaneous appendages (hair, horn, claws) of domestic animals derives mainly from the pigment melanin (23). The pigment occurs in granules in the epithelial cells of the basal layer of the epidermis (23). Other locations in the body, such as the mucous membranes of the mouth, the muzzle and the meninges, normally contain melanin in varying degree (23). The eye contains a pigment layer at the junction of choroid and retina, on the posterior surface of the iris (pars retina iridica), and likewise on the anterior surface and mesoderm of iris (23).

Since the basic cellular steps in the production and distribution of melanin in domestic animals have not been demonstrated, evidence accumulated in work with laboratory animals will be cited for the understanding of these basic principles. There are probably other skin pigments besides melanin, but those are considered of minor importance in mammals. Therefore, the ensuing discussion will be restricted to melanin.

I. Site of Production and Distribution of Melanin

The site of melanin production in the mammal has been shown to be the melanocyte. Two types have been distinguished: the dendritic melanocytes which arise from the neural crest and migrate into many tissues, and the epidermal melanocyte in the pigment layer of the retina (2). Melanocytes undergo mitotic division and maintain a horizontal network of a type specific cell line at the dermoepidermal junction (14). The melanocyte cell has been described as containing a system of membranes similar to those of secretory cells (14).

Though many different colors are known in the mouse, only two kinds of melanin granules have been demonstrated: the black, spherical granule of

eumelanin and the yellow, round granule of pheomelanin (43). Although the presence of eumelanin or pheomelanin determines hair color, the genetically controlled variation in size, shape, and distribution of the melanin granules creates visible color differences in the appearance of hair (43). Melanin was revealed to be an amorphous pigment of protein origin, probably arising from tyrosine, phenylalanine, and tryptophane by the action of the enzyme tyrosinase. On the basis of electron microscopic studies (48), it was proposed that the development of melanin granules in the mouse progressed through different stages which are controlled by the color genes of the individual. Biosynthesis of polypeptides takes place at the ribosomal level. At the intermediate stage, the premelanosomes are assembled. The final stage is the biosynthesis of melanin and its accumulation inside the premelanosome constituting a melanin granule. This procedure occurs in the melanocyte just beneath the epithelium. The final end products, the melanin granules, are transferred by pinocytosis into the cytoplasm of the epithelial cells in the basal layer (14). The hairs take up melanin granules apparently in the same manner, which are mainly deposited in the cortex.

II. Interrelations of Hormones and Pigmentation

Several hormonal factors control normal pigmentation in mammals (27). The intermediate lobe of the pituitary produces two polypeptide hormones, the melanocyte stimulating hormones (M S H) - alpha and beta. These hormones are excreted in the urine at a similar rate in Caucasians, Negroes and albinos (27). Other endocrine glands such as the adrenal, thyroid and gonads also contribute to the regulation of pigmentation.

Pigmentation in mammals depends in some unexplained manner upon sex hormone control. Evidence from investigation of melanomas in man has suggested repeatedly the interrelationship of sex hormones and pigment cells (10). The influence of sex hormones on pigmentation also has been demonstrated by the appearance of the "ghost pattern" in maturing albino cattle (8, 39).

Certain neoplasms of the endocrine system in man are known to be associated with disorder of pigmentation. The resulting pigmented dermatoses are not due to any abnormal pigment, but to altered amounts and distribution of normal melanin (10).

III. Basic Cellular Defect in Albinism

Little is known in domestic animals about the basic defects in albinism. Therefore, evidence accumulated in laboratory animals and man will be cited in order to give a better understanding of this hereditary defect.

The various coat colors such as black, brown, red, and white do not indicate different pigments but rather different distribution and concentration of melanin in skin and hair. Pigmentation is controlled by the action and interaction of genes. Mutant genes which cause diluted or white coat color in mammals have been known for a long time and are common in laboratory animals. In one study hair pigment of the mouse was studied by means of counts, measurements and color determination of the pigment granules in the cells of the medulla and cortex of various portions and successive levels of the hair shaft (43). Included in the investigation was the albinos series: $C \succ c^{ch} \succ c^{h} \succ c^{e} \succ c$. According to this study, the action of the albino genes resulted in a quantitative change in the degree of pigmentation.

In another study, size, shape, number and distribution of pigment granules

were controlled by color genes (29). Two pigment mutants of the mouse, namely, "leaden" (ln ln) and "dilute" (d d) were used. The coat color of these mutant mice was diluted. The genes had a distinct effect on the shape of the melanocytes. The "leaden" and "dilute" melanocytes had fewer and thinner dendritic processes; the distribution of the melanin granules was nucleopetal. Electron microscopic studies demonstrated the color genes in mice to have a definite effect on number, size, and distribution of the melanin granules. In all cases investigated, the sequence of fine structural changes and the development of the individual granule were the same. The exception was the albino gene, for the production of melanin granules stopped at the premelanosome ("ghost granules") stage.

Originally, the basic defect in albinism was thought to be a lack of dopa-oxidase. However, the absence of another enzyme, tyrosinase, has been fairly well established as the biochemical lesion of general albinism (9, 53).

The exact chemistry of melanin is not known, but it is considered by many to be formed from the amino acid, tyrosine (9, 53). The effect of genetic substitution of color genes on the incorporation of tyrosine into the melanin of the mouse skin has been studied (9). This report demonstrated the expression of coat color genes at the cellular level. The allelic genes of the C - locus controlled a decrease in tyrosine uptake in the sequence ($C > c^{ch} > c^{h} > c^{e} > c$).

The values for heterozygotes were intermediate between CC and cc, thus indicating the absence of dominance at this level. Brown (bb) had greater uptake than black (BB), agouti decreased the uptake, and leaden (ln ln) and dilution (dd) had no effect upon tyrosine incorporation.

IV. Occurrence and Inheritance of Albinism

A. Laboratory Animals

1. Mouse

In mice, rabbits, and many other animals, an important locus with two or more alleles, the C locus, regulates color expression of the animal. The same locus is presumed also for cattle (39). The genotypes CC and Cc allow the production of pigment and color, depending on the remaining genotypic background. The genotype cc, however, works epistatically to prevent the expression of other color genes. The resultant individual is an albino with white skin and pink eyes.

The albino series in the mouse consists of five alleles: Full color C, intense chinchilla c^{i}, chinchilla c^{ch}, extreme dilution c^{e}, albino c (16, 49). As mentioned above, C is completely dominant over the remaining alleles at this locus. A stepwise reduction of yellow pigment takes place first, then the black pigment is reduced. Albino mice (cc) look alike, regardless of the other color genes they carry; they are white and have pink eyes.

Estimation of the mutation rate of the albino locus yielded an average forward mutation rate of 11.0×10^{-6}, and an average reverse mutation rate of 2.7×10^{-6} (45). Another estimate was in the same range, namely, 7.5×10^{-6} average forward mutation (44).

There are a number of other color genes which not only influence color but also have pleiotropic effects on skeleton, the formation of the eye and the central nervous system. Since they may have relevance to investigations in cattle, some will be considered here.

A syndrome "varitint-waddler mouse" has been described in which the clinical observations were disturbance of equilibrium, involuntary head movements, deafness, and pigment defect in the fur (7). The coat color modifications consist of three types: areas without pigmentation, areas with partial and progressive dilution of coat color, and patches of unchanged coat pigmentation. Heterozygous mice have irregular spots of white hairs on body and head, or roaning effect, whereas homozygous animals are white with the exception of small isolated patches of color. Both the heterozygote and homozygote show other components of the syndrome, but in the homozygous condition the expression is more severe and a high embryonic mortality occurs. From experimental matings, a simple autosomal dominant gene was shown to be respensible. The gene was not allelic with piebald pattern and dominant spotting genes.

Evidence was presented pertaining to the relation of iris abnormalities, disturbances in choroidal pigmentation and piebald pattern of various genotypes in mice (13). In piebald mice, the choroidal pigmentation was generally defective. A relationship between dominant white and microphthalmia in mice also was suggested (17).

The white coat areas in the patterns listed above were shown to result from arrested penetration of the melanoblasts which were unable to migrate normally through skin which had beceme too differentiated. As a result, portions of the skin could not be penetrated by the melanoblasts (31, 47).

2. Rabbit

Interesting contributions to the genetics of color come from investigations in the rabbit. As in the mouse, there is a set of multiple alleles at the albino locus: full color C; chinchilla, c^{ch}; Himalayan, c^{h}; and albinos, cc (49). The Himalayan rabbits, $c^{h}c^{h}$, exhibit an interesting temperature

dependent mutant. The same effect resulted from sympathectomy (54). Elevation of the cutaneous temperature and sympathectomy result in inhibition of pigment formation. However, the mode of action appears different since sympathectomy caused inhibition of normal melanogenesis.

The genetic relations between eye color and pigmentation have been demonstrated in the rabbit (34). The color factors C E B D A have been determined and in this constellation are responsible for wild rabbit (A) color pattern; the iris of such animals is fully pigmented. Replacement of allelic genes caused several coat and iris patterns. The four factors E B D A and their alleles allow 16 possible combinations. However, the change of A to a and E to e has no visible effect on iris pigmentation. Replacement of B by b, on the other hand, has a small effect on iris coloration. Animals carrying the d gene instead of the D gene show marked dilution of coat and iris color. In the albino series, 6 alleles are listed (34). Besides the color factors, modification factors are known which also influence iris coloration.

There is a correlation between the degree of marking or spotting and eye-color. The recessive Vienna blue-eyed white rabbit has a white coat with reduced pigmentation of the iris. The same is true for recessive spotted Dutch rabbits where the extremely white animals show heterochromia irides. The latter does not occur in the patchy dominant type of spotting in English rabbits which have dark eyes. In crosses of English with Dutch, the coat color pattern was that of English rabbits but the eyes showed partial or total heterochromic irises. Histological investigations of these eyes revealed a lack of pigmentation in the anterior mesodermal layer of the iris whereas the posterior ectodermal layer still produced pigment.

3. Guinea-Pig

The coat color of guinea-pigs depends on the production of pigment granules resulting in either sepia, brown, or yellow; absence of pigment results in white (61). White coat in the guinea-pig may have three causes: failure of the melanocyte, or its precursor, to migrate to the dermo-epidermal junction; death of the melanocyte; or defective melanogenesis (61). The E locus in the guinea-pig differentiates between the production of eumelanin and pheomelanin. The C locus was shown to be responsible for tyrosinase activity. This series, the albino series, exhibits dominance within its alleles (61). Since the C locus affects tyrosinase activity, a defect here is related to amelanotic melanocytes which are not melanogenic (61). Other pigmentation defects in the guinea-pig are known also which result from absence of melanocytes (60).

B. Cat

The set of albino alleles in the cat include: full color, C; silver, c^{ch}; Burmese, c^{b}; Siamese, c^{s}; and complete albino, c (42). The phenotypes of the series listed above show a gradual reduction in pigmentation. Yellow is reduced early in the series, but black is affected later, thereby causing the lower members of the set to be increasingly thermosensitive. Little research has been done on the correlation between eye color and body color in the cat and other domestic animals. A few other color factors which appear to be related to albinism have been described. Completely white cats with either yellow, blue or heterochromic eyes are caused by a dominant gene. The expression of the gene is irregular and in the heterozygous condition shows either complete or partial expression (60). The homozygous state is lethal in the fetus (19).

C. Dog

A similar pattern has been established for albinism and related defects in the dog (3). The albino series is as follows: full color, C; c^r, partial albinism; c^d, white coat with dark nose and eyes; c^b, pale greyish with pale blue eyes; and c, total albinism Dominance also appears to be present but is not complete.

The triad of white coat color (or a patterned white and colored coat), discoloration of the iris and sometimes deafness, has been reported on several occasions in different breeds of dogs (32, 50, 59). The most extensive study included 35 dappled dachshunds, 9 merled collies, and 3 miniature merled collies, which had heterochromia irides (50). The tapetum always was either absent or rudimentary. The iris anomalies on the other hand, were inconsistent ranging from normal coloration to either unilateral or bilateral sectorial, or complete, discoloration of the iris. The dappled or merled animals were known to be heterozygous. Breeders reported matings of dapple to dapple resulted in litters of self-colored dogs, dapples, and extreme dapples. The homozygous state of "extreme dapple" showed a high degree of depigmentation of coat color which was associated with eye malformations such as microphthalmia, depigmentation of the iris and lack of tapetum lucidum (28). The mode of inheritance of wall-eye associated with merling or dappling coat pattern in dogs was found to be a dominant with incomplete penetrance (32, 50). The gene in the heterozygous condition produced coat color variation (merling, dappling), discoloration of the iris and tapetum anomalies. The homozygous state caused pathological conditions such as gross ocular anomalies, depigmentation of coat and, occasionally, deafness (28).

D. Pig

The occurrence of albinos in registered Hampshire swine has been reported (41); the eyes are red and the coat color, light sepia. The condition proved to be caused by a recessive gene.

Heterochromia irides in pigs furnishes an interesting type of inheritance. The gene is incompletely dominant and is manifested in about half of the heterozygous progeny. The other animals receiving the gene show no phenotypic deviations but pass the gene on in a dominant manner. No particular coat patterns seem to be related to the occurrence of wall-eyes. Although merling in pigs is known, the status of the eyes has not been recorded. The frequency of heterochromic irises in pigs has been estimated to be between 5-7% (5, 59).

E. Horse

White coat color in horses may result from various genes. It is particularly obvious here that albinism involves not only a genetic problem but also a semantic problem: what is equine albinism? Although very sophisticated studies are available on the horse, there appears to be a definite lack of histological and clinical investigations.

No color gene in horses has undergone an albino mutation (6). However, some other genes responsible for the dilution of coat color and the related pigment reduction in the eye are listed. Dominant dilution (D D) in the homozygous state causes cream body color and blue eyes in AA or Aa, BB or bb background. Body color is even more dilute in AA (or Aa) in a bb background. The skin appears pink; the eyes, blue. There is yet another gene which affects coat color and eye color. This is the dominant white gene which proved epistatic in crosses with all colors of horses; the gene probably was lethal when homozygous (6).

Heterochromia irides also occurs in horses. Pigmentation in the iris varies greatly, ranging from only small white areas in the lateral, medial, or central portions up to the completely white circular form (21, 58). In the splashed white head color pattern, the white coat areas occurs mostly on the ventral aspects of the body. When greater portions of the head are white, a "glass" or "wall-eye" is usually present. The inheritance of heterochromic irises was traced in several breeds, particularly in two lines with fairly close inbreeding. Two genes caused "wall-eye" in horses and these were correlated with a white coat color pattern. No ocular abnormalities of any other kind were described. Horses with heterochromic irises had normal vision and seemed to have little or no increased sensitivity to light. Some other reports indicated recessive cases and still others, dominant with no sex linkage (59).

F. Man

1. Complete General Albinism

Knowledge of albinos can be traced back far into history of man. Several forms of albinism are distinguished clinically and genetically (14). The incidence of the complete type of albinism in man is reported to be one in every twenty thousand births (53). No estimates are available for other types of albinism, such as incomplete and partial albinism, but these appear to be rare (25). To summarize the clinic and genetic findings in man, Table 1 is included.

A variety of anomalies can be responsible for the inability to form pigment; one of these is a lack of tyrosinase. Amelanotic melanocytes apparently are present in the skin of human albinos (53). The enzyme tyrosinase is inactive in the albino skin (25). In addition to complete albinism, other albinotic pigmentary deficiencies are described. The biochemical relationships between these partial forms and the complete form have not been elucidated.

2. Incomplete and Partial Forms of Albinism

Less is known about incomplete and partial forms of albinism in man and no gene frequency estimates were found in perusal of the literature (25). The characteristics of the two forms are listed in Table 1 . Two syndromes, the Chediak-Higashi and the Waardenburg, which belong to this general symptom complex, are considered separately since they appear to be of special interest as biological models.

3. The Chediak-Higashi Syndrome

One partial form of albinism was reported to be part of the lethal Chediak-Higashi syndrome, characterized also by increased susceptibility to infection, predisposition to a peculiar type of malignant lymphoma, and abnormal granulation of leucocytes (38). Necropsy examinations revealed massive splenomegaly and neurologic symptoms. Histopathological lesions were disclosed as infiltrations of histiocytes and immature lymphocytes in heart, liver, spleen, kidneys, central nervous system, and lymph nodes (38). The ocular lesions were reported as pigment deficiency of the iris and infiltration with immature lymphocytes (51). The skin lesions were absence of pigment (52). This syndrome has a low frequency in man; of 82 albinos investigated for the granular leucocytic anomaly none had it (52).

4. Waardenburg's Syndrome

Another syndrome in man associated with partial albinism was recognized as a combination of six chief characteristics: white forelock (a form of partial albinism): partial or total heterochromia irides; complete deaf mutism or an incomplete degree of congenital deafness; a malformation of the face resulting in a lateral displacement of the medial canthi and lacrimal points combined

with blepharophimosis; prominent broad root of the nose and a growing together of the eyebrows at their medial portion (55). The syndrome proved to be inherited in an autosomal dominant manner, but the different components possess different penetrance. White forelock has a penetrance of 17%, deaf mutism 20%, heterochromia irides 25%, whereas the other components are considerably more constant. Growing together of the eyebrows had a penetrance of 45%, a broad root of the nose was manifested in 78% of the cases, and lateral displacement of the puncti and canthi was the most frequently encountered anomaly occurring in 99% of the 14 families with 164 probands. The incidence of Waardenburg's syndrome was estimated at 2.5% of the congenitally deaf individuals in the United States (12). Each of the components of Waardenburg's syndrome has been recognized as a separate hereditary trait with dominant as well as recessive type of inheritance.

G. Cow

No estimates of the gene frequencies relating to albinism in cattle populations are available. As early as 1920 an albino herd was described (11). These albinos showed no pigment in the skin, eyes, horns, or claws and the eyes were extremely sensitive to light. The parents of the albinos exhibited normal Holstein coat color. This suggested a recessive gene, but further data indicated dominance, as an F_1 albino bull sired only albino calves when mated to 20 unrelated grade Holstein cows (11). Furthermore, the matings of albino females to a Holstein bull produced only albinos. It should be mentioned that the breeding records of this herd had been lost and the data presented were based on memory. However, the author did not question the correctness of the report given by the owner of the herd (11).

A single case of a female calf with complete lack of pigment in skin, hair,

and iris was reported (24). The pupils had a red color. The breeding test indicated a recessive gene since the mating of an albino female resulted in a normal offspring.

Another herd of albinos showed the following characteristics: complete lack of pigmentation in skin, iris, and hair at birth; at sexual maturity, some pigment could be observed and this phenomenon was designated as "ghost pattern" (8). Histological examination of hairs from the white areas revealed no pigment in the cortex whereas those from the lightly pigmented areas had a varying amount of dark pigment irregularly scattered throughout the cortex. Sections of eyes from two animals were studied. No pigment was found in the retina whereas the iris and ciliary body showed some pigmentation causing the pupils to be pink but the irises, grey. Two animals were purchased from this herd for breeding tests. The mating produced an albino bull calf. Albinos were mated to black and white, red and white segregates from Holstein-Angus crosses, and also to a red roan Shorthorn bull. All calves from these matings were black and white. The data obtained indicated a recessive gene for extreme reduction of pigment. Milk production and vitality of the albino cattle was not less than the normal.

The occurrence of 22 albino animals in Brown Swiss cattle was investigated in the German province of Wuerttemberg (4). Fourteen animals were closely investigated and one female and one male were purchased; the other cases were later traced. The two albino animals were mated and produced a male albino calf. These three animals were later slaughtered and samples were taken from the eyes, skin, horns, claws, and hairs. These tissues were all unpigmented. The iris was white with a pinkish shine, the pupils were red and photophobia was extreme. These albino cattle showed no decrease in fertility or other economically important traits. The authors concluded that albinism is a recessive trait since test mating of albino x albino resulted in albino and albino

x normal resulted in normal coat color. Furthermore, pedigree studies were done and in herds in which albinos occurred, common ancestors could be traced.

Three albino animals were reported in a Holstein herd. At the date of investigation, two yearlings were alive (22). The skin was described as pinkish and the muzzle, claws and horns, unpigmented. The hair was creamy-white and no ghost pattern was observed. In daylight, the iris was greyish-blue and the pupil black, whereas in twilight, the pupils had a pinkish shine. Both animals were photophobic. The inheritance was thought to be recessive since both parents of all 3 animals were related.

The results of 43 matings demonstrated to Peterson that albinism was inherited as a simple recessive (39). In all albino x albino matings, albinos resulted. The mating of heterozygote and homozygote gave almost the expected proportion of albinos and colored. Crosses of albinos with normal animals always gave normals. Further, it was shown that ghost pattern was due to structural anomalies of the hairs rather than different degrees of pigmentation. The appearance of ghost pattern was associated with the factor for black (B) and was obvious at sexual maturity.

From Japan came a report of three albino Holstein calves (30) from a common sire and whose ancestors had been imported from the United States. In Wisconsin and Minnesota, the occurrence of albinos had been reported in these families.

In the Murbodner breed in Austria, a single albino calf was observed (45). This calf, the result of an accidental mating of a son to his dam, showed no pigmentation at all and the iris was pink. Comparative body measurements and skin thickness did not reveal any differences from normal.

Three cases of albinos were recently reported in Brown Swiss cattle (57). In each case, the parents exhibited normal coat color. Breeding experiments

were not carried out but a single autosomal recessive factor was presumed. Since the cases were related to cases earlier, sporadic reappearance of the same mutation was considered. The cattle were described as having pink eyes, pink skin, lack of pigment, and photophobic.

Albinism has also been reported in Hereford cattle (35). Three albinos were observed in a small herd of registered Hereford cattle where a young bull was mated to two of his full-sisters and four of his half-sisters. Several animals were acquired from this herd for breeding tests and from the brother-sister matings, three albinos resulted. The affected offsprings had light pigmented areas on the inside of the hind legs but no evidence of ghost pattern. Clinically, the calves showed phtophobia but were otherwise normal. Blood types of the sires and dams of the albinos were determined and were similar. Albinism and dwarfism were observed together in the same animals, but it was felt that the two traits were independent (18). A blood abnormality was found in these partial albinos which was considered to be identical to that observed in the Chediak-Higashi syndrome of man (37). Increased susceptibility to disease was also observed. Breeding experiments performed with these cattle revealed a recessive gene (35).

Chemical investigations of the pigment content of bovine hair showed melanin was present, not only in white hair from colored Herefords, Holsteins, and Guernseys but also in albino hair (56).

In conclusion, the findings of the various authors investigating bovine albinism are summarized in Table 2 . Albinism, as well has heterochromia irides, has been known to occur in certain species of domestic animals (1, 15). Albinism has been reported on a number of occasions in cattle but heterochromia irides has not been described (20, 26). Perusal of the literature failed to reveal any studies concerning the correlation of eye and body color in cattle.

MATERIAL AND METHODS

I. Definitions

Because of need to compare work of other authors with this investigation, the terms albinism and heterochromia irides are defined here. The definitions are modifications of those employed in man (15) and are based on reported cases in the literature (see Table 2), and on experience resulting from clinical and histological examinations of bovine cases.

A. Albinism:

1. Complete general albinism:

Complete general albinism in the bovine is a congenital defect characterized by pinkish skin, pinkish muzzle, white hair, and clear yellowish claws. The most striking findings in bovine albinism are the eyes, which exhibit, in the complete general form, white conjunctiva, white iris with pinkish shine, and an albinotic pupillar reflex.

2. Incomplete general albinism:

This form shows the same features as the complete type but the iris has a blue color due to the presence of pigment in its posterior layer.

3. Partial albinism:

Partial albinism in the bovine is characterized by a grey iris, white skin and hairs, and partial pigmentation of the coat in the form of patches and or spots. Partial albinism is also expressed by the appearance of "ghost pattern" in the coat.

B. Heterochromia irides

Heterochromia irides is an ocular condition in which a portion of an iris exhibits a different color than the remainder or when both irises are of different colors. The general body color may be white, with or without color spotting.

II. Nature of Investigation

Albino animals, animals affected with heterochromia irides, and normal animals, were inspected closely in one or both of two herds (Herd 1 and Herd 2). Although not all animals could be examined ophthalmoscopically, many were.

For histological studies hair samples were taken from animals in both herds, together with skin biopsy material from one animal and tissues from four animals at necropsy. These latter tissues included: eyes, eyelids, muzzle, soft palate, skin, hairs, brain, hypophysis, thyroids, adrenals, kidney, liver, and spleen. Tissues were fixed in 10 percent buffered formalin and processed according to standard histological procedures. The following stains were employed: Hematoxylin and eosin for skin, hair, eye, endocrine glands, brain and hypophysis; Fontana-Masson for eye, skin and hair samples; Weigert's Resorcin-Fuchsin and van Gieson for eye sections.

Herd histories were obtained in both cases and where possible, the data were subjected to statistical analyses. From Herd 1, a bull and a heifer were acquired for breeding trials.

III. Investigational Procedures

Since experimental work with cattle is expensive and handling of cattle, is difficult and inconvenient for the owner, the investigational procedures varied in the two herds. In addition, the experience gained in Herd 1 and the greater

cooperation of the owner of Herd 2 resulted in a more detailed study of that herd.

A. Herd 1

This herd was visited on a cloudy June day 1965 and twenty-one albino animals, bulls, cows, and calves were examined closely. The remaining animals in the herd were running on pasture and could only be inspected from a distance. Two animals, a young bull and a heifer, were purchased and tranported to the University where they underwent a detailed clinical examination and were used in breeding trials.

B. Herd 2

Although information was collected on a number of visits to Herd 2, most was collected on two visits, one in October 1965 and the other in March 1966. On the first of these, an albino cow and 11 colored cows with heterochromia irides were inspected, including an ophthalmoscopic examination. On the second visit, a cold rainy overcast day, the entire herd, with the exception of the herd bulls and all but four calves, was run individually through a squeeze chute for examination. In addition to the coat color, the degree and location of iris discoloration and of eyelid pigmentation of both eyes was recorded. The eyes of each abnormal animal were photographed in color and 2 x 2 slides made for record and future study. The difficulties encountered previously in examining the eyes of albinos and other cattle were minimized by the absence of the usual bright Kansas sunlight.

Because the owner was somewhat uncertain of the ancestry of some of the animals examined, arrangements were made to blood type a selected group of 31 animals to confirm parentage information.

The animals included were the albinos, 22 animals with heterochromia irides, and 8 animals chosen randomly from among the normal animals; blood samples and blood smears were taken. During examination of each animal, the owner listed the names; later recorded the parents and grandparents.

Two other animals also were examined; one, an albino steer calf and the other, a cow with heterochromia irides. These animals had been purchased for detailed anatomical and pathological studies.

RESULTS

I. Herd 1

A. Herd History

Since the owner does not keep adequate records, the history is drawn entirely from his recollections. The herd descended primarily from grade Herefords although a few grade Holsteins and Guernseys have been included. The first albino heifer was bred to a grade Hereford bull and produced a white, glass-eyed bull. That calf was raised, mated with grade Herefords, and produced not only normal calves but also white, glass-eyed calves, some with a few dark spots in their hair coats. From one of those matings, or from matings a year or two later, another white, glass-eyed bull was saved. That bull, Bull X, is pictured in Figures 1 and 2 . Alive yet, he has been mated extensively with grade Herefords, Holsteins, and Guernseys and with daughters of either the first albino bull or of one or two other yearling white glass-eyed bulls later slaughtered, or with both. He has sired only white glasseyed progeny (Figure 3 and 7). About 10% had small colored hair spots, usually on the shoulder, and also may have had irregularly splotched irises, which the owner called "spotted eyes". Bull X also was mated with Holsteins in a neighbor's Holstein herd;

there, too, he sired only white, glass-eyed progeny.

Another white, glass-eyed bull (Bull Y) was reared recently as a herd sire; his parents were a colored grade Hereford cow and one of the white herd sires. He has not bred true. When mated with grade Hereford cows, half of the progeny were colored and half, white and glass-eyed. When mated with glass-eyed cows, only white progeny resulted. Some of white progeny had few dark hair spots and spotted eyes; most such have been eliminated from the herd because the owner prefers the pure white, glass-eyed kind.

Today, the herd consists of about 90 animals; about 60 are white and glass-eyed; about 30 are colored, predominantly like Herefords. The white, glass-eyed cattle are all descendants of the original heifer. Although the white cattle show extreme photophobia and some, according to the owner, deafness; they are not defective in other respects. No cancer eye nor pink eye has been noted. With respect to coat color, none of the colored animals evidenced any roaning like that of the Shorthorn nor extreme dilution like that or the Charollais cross-bred, nor were any animals all white with colored points like those occasionally found in the recessive white spotting breeds, such as the Holstein.

B. Description of Albinos

A group of 21 animals (5 cows, 10 yearling heifers, 2 young bulls, Bull X and 3 baby calves) were examined closely in a small lot (Figures 1 to 6). Every animal was pure white; no spots nor lightly pigmented areas were observed anywhere on the bodies of these animals. The skin was pink and almost transparent; the muzzle, eyelids, vulva, anus, and udder were pink, almost flesh colored, and lacked pigmentation. The hooves were clear yellow. The hairs were white, fine, shorter than usual and wool-like. The eyelashes and the hairs in the ears and switch also were white. Ghost patterns observed in other albinos have never

been seen (39).

With the exception of two calves all other white animals examined at greater distances appeared similar to these 21 examined closely. The two exceptional white calves had a few dark brown spots on the shoulder ranging from about 2-6 inches in diameter.

The eyes of the 21 cattle did not fit closely the descriptions previously published for albino cattle, nor did they resemble closely the pink eyes of the albino rat, mouse, or rabbit (Figures 8 to 11). The eyelids, the nictitating membrane, and the conjunctivae were white to pink in color and apparently pigmentless. The conjunctival blood vessels were distended and clearly visible (Figures 8 to 11). The iris in its central part around the pupil was pale blue but toward the periphery, pale white. The boundary between the two areas was variably irregular. The white color extended almost to the medial and lateral angle of the pupil (Figures 8 to 11). No pink irises were observed. The iris color of glass-eyed cattle was compared with that of normal Holsteins, Herefords, Shorthorns and Charollais. The latter had heavily colored irises including one white Shorthorn which had very dark blue irises and a Charollais (white) which had light brown irises. The anterior surface of the iris seemed folded, a condition caused by protrusion of the peripheral arteries and their radial branches. Although there was some slight variation in the color of the irises of different animals, both eyes of each animal examined were seemingly identical. Most other animals examined from greater distances seemed also to have concordant iris color. However, three animals were observed with discordant eye color. The two white calves with small colored hair spots also had spotted irises which were not identical in the same animal. Another white calf had a pale blue left iris and a grey right iris. A fourth calf with concordant iris color had dark blue irises. None of the colored animals observed had abnormal irises.

The pupils were elliptical and extremely narrow even on cloudy days (Figures 8 and 10). In daylight, the pupils appeared dark brown, an unusual characteristic for true albinos. Two animals purchased for observation and breeding were examined minutely. Their pupils too in daylight appeared dark brown. However, in a darkened room, the pupils were a muddy pink. Ophthalmoscopic investigations revealed a lack of pigmentation in the fundi of the eyes of both animals. In the normal eye, the greatest part of the fundus is occupied by a brilliant green tapetum lucidum and a small band of tapetum nigrum. In these glass-eyed cattle the fundus was a bright evenly distributed orange color. Blood vessels usually quite apparent in normal cattle were indistinguishable for the orange tinge hid the tangled network of vessels.

C. Histology of Biopsy Specimens

From the purchased heifer one eye was enucleated and several skin and hair samples taken. Histological investigations of this enucleated eye revealed several abnormalities (Figures 10, 12, and 13). The iris leaf was somewhat hypoplastic. The posterior layer of the iris was pigmented but not so densely as that of normal eyes. The remaining layers of the iris were devoid of pigmentation (Figures 14 and 15). The black corpora nigra on the pupillary margins were smaller than usual. The pigmentation of the posterior layer of the iris extended on to the ciliary body and over the ora ciliaris retinae into the peripheral parts of the retina (Figures 13 and 14). The remainder of the retina (pars optica retinae) was completely unpigmented (Figures 14 and 16).

In the sectioned half of the eye, the choroid layer, usually densely pigmented in normal cattle, had no pigment. The other half, which was cleared in an alcohol series and placed in oil of wintergreen, was completely transparent with the exception of the posterior layer of the iris and the peripheral part of

the retina. All layers of the retina were present and seemingly normal in structure. However, the tapetum fibrosum was anomalous in structure.

Skin samples taken by biopsy and hair samples also were investigated histologically. No pigment could be found in the skin samples. Nor was any found in hair samples, either on cross section or on whole mounts, stained or unstained, in the cortex or in the medulla.

D. Breeding Experiments

The bull purchased was bred to 4 cows: a Hereford dwarf, two Jersey cows, and a Holstein. The Hereford dwarf produced a normal appearing Hereford bull calf and one Jersey cow dropped a bull calf with normal Hereford pattern.

However, the Holstein cow delivered a heifer calf which is all white and exhibited heterochromia irides (Figures 17, 18, and 19). Muzzle and skin are pinkish. The fundus of the eye is typical of an albino; the pupils have an albinotic reflex. The conjunctivae are pigmentless. Both irises differ in their appearance. The left iris is grey at its peripheral part but has a blue central area which has an irregularly shaped white area in its lower part (Figure 18). The right iris exhibits similar features yet the white spot in its lower part is not so large as on the left side (Figure 19).

The other Jersey cow also delivered an albino, a bull calf, which in its external appearance is similar to the one described above. Yet the appearance of the iris is somewhat dissimilar, for the heterochromia is expressed as two rings of color, an outer ring of grey and a smaller inner blue ring.

E. Necropsy and Histological Findings

The two normal bull calves were available for dissection; the two albino calves will be raised for further experiments.

Both bull calves were found to be normal at necropsy with the exception that the calf dropped by the Jersey cow had a large cystic residual hypophyseal lumen.

Histological sections of central nervous system, endocrine glands, skin and hair revealed no deviations from normal.

II. Herd 2

From this herd, 81 animals were examined. They comprised three phenotypic groups: a group of two albino animals, a group of 25 animals with normal coat colors and patterns but with heterochromic irises, and a group of 54 animals normal in all color characteristics.

A. Description of Animals

1. Albino Animals

The two animals were mother and son. The mother (Figure 20) was the first pure white animal ever observed in this herd of 110 Herefords. She had no spots or ghost pattern. Her skin was pink, particularly noticeable on the muzzle, eyelids, ears, udder, vulva, and anus. Both irises were bicolored; the central part around the pupils was a faint blue, while the peripheral, broader ring was light grey in daylight; thus the iris appeared doubleringed (Figures 22, 23, and 24). From a distance, the iris seemed to protrude conically into the eyeball. On close examination, the peripheral part of the iris had small irregularly shaped white areas and a few small dark spots, one-half to 1 mm. in size, intermingled in the grey. Fine dark stripes extended from the root of the iris to its center. The two irises were slightly discordant in color.

The pupils were narrow and almost rectangular in shape. In daylight, they

appeared brown, but, under artificial light, pink. The conjunctiva, selera, nictitating membranes, eyelids, and eyelashes were pigmentless. Opthalmoscopic investigation revealed a faint orange fundus. Photophobia was pronounced.

The albino cow's son (Figures 21, 27, and 28) had a white coat, too, but on his right shoulder was a dark brown spot, about two inches diameter. No other color patch could be detected anywhere on the hide or claws. His eyes differed from those of his dam in that the greyish peripheral ring was interrupted by pale white splotches (Figures 25 and 26). Hence, the iris has a piebald appearance. His fundi also showed a pigment deficiency.

The albino son was one of four sons produced by the cow. The two older sons, sired by a colored registered Hereford bull, were normal. The younger son, sired by an Angus bull, had white face and black coat. When less than two months old, his eyes appeared somewhat lighter than normal.

2. Heterochromia irides

The most remarkable finding in this herd was binocular heterochromia irides in otherwise normal Hereford cows. The irises like the albino's consisted of two concentric rings of color, but were darker. The central ring was blue and contained whitish regions; the peripheral ring was brown (Figures 42 to 50). From a distance of 10 yards, the irises also seemed to protrude conically into the eyeball. Although the animals were photophobic, their vision seemed unimpaired. The pigmentation of the fundus was reduced; the normally brilliant lustrous green of the tapetum was replaced by a very light faded green.

Although in half of the 25 animals with heterochromic irises, the eyes were alike, the other half evidenced discordancy. Eight showed a slight discordancy in degree of heterochromatism, two a marked discordancy, and two, the

extreme: one normal eye and one heterochromic eye. These variations are noted in Table 3 where the location of the whitish splotches are indicated by numbers as on the face of a clock. The degree of heterochromatism was scaled on a 5 point scale, in which V represented the extreme, a clear watery-like iris seen in one cow. In 6 animals, the irises were uniformly discolored but not splotchy.

With respect to eyelid pigmentation, 15 animals had white eyelids. The remaining ten had some degree of pigmentation; four had partially pigmented eyelids and six, completely pigmented eyelids. Of the latter, four had extensive red hair patches surrounding the eye. All animals had the usual Hereford coat color and pattern. However, the cow with the greatest degree of pigment reduction in the irises was very light colored, being fawn yellow in color.

3. Normal Herefords

The remaining 56 animals had coats and irises of normal color. They include 54 cows and two breeding bulls: the sire of the albino cow as well as the sire of the albino steer. Because of time restrictions, only six calves were examined. They had normal coats and irises.

B. Macroscopic and Histological Findings

1. Albino

The albino steer was slaughtered for human consumption. During the procedure, gross findings were recorded and sections of skin and endocrine glands were collected, together with both eyes.

The only gross finding was a large cyst located in the hypophysis (Figure 30); the other organs appeared normal.

The hypophyseal cyst was 1.5 x 1 x 1 cm and filled with yellowy watery

fluid. This cystic residual hypophyseal lumen replaced a large portion of the intermediate lobe and parts of the anterior lobe. It was lined by cuboidal epithelium with brushlike borders. Histologically, the endocrine glands were normal.

Both eyes revealed a change in the color of the fundus; the normal glistening green of the tapetum was replaced by a dull grey with a greenish tinge, and the tapetum nigrum was only slightly grey (Figure 29). Grossly, both eyes differed in iris color; this was confirmed on histological examination. In the blue central part of both irises, the stroma and anterior layer were unpigmented, whereas the retinal layer was pigmented (Figure 31). The white areas of both irises had the same histological features as the blue central part but revealed as an additional one, hyperpigmentation of the posterior layer (Figure 32). However, the grey areas exhibited two distinct histological features. In some sections the anterior layer and the stroma had reduced amounts of pigment, whereas the posterior layer was hyperpigmented (Figure 33). In other sections, the stroma was devoid of pigment in its posterior parts but had clumped large pigment aggregates in the anterior portions (Figures 34 and 35). The posterior layer had normal to slightly reduced pigmentation. Hence, two distinct patterns of pigmentation may give rise to a grey iris: one, reduced pigmentation and the other, abnormal size and distribution of pigment granules.

Pigment, though in reduced amounts, was present in the other normally pigmented structures of the eye, such as the ciliary processes and retinal pigment layer. The choroid and sclera, however, had no pigment.

Skin sections taken from the brown spot had pigment granules (Figures 39 and 40). Sections of skin from the eyelids, face, neck, shoulder, along the ribs, the lumbar region, and the distal leg regions, and sections from the muzzle, lips, and palate were devoid of pigment (Figures 36, 37, and 41).

However, all skin sections revealed a slight hyperkeratosis, a variable degree of infiltration of eosinophils and a moderate number of macrophages in the subcutis (Figure 38). These were more marked in regions exposed to sunlight indicating a photosensitivity which would not be found in a normal animal under comparable environmental conditions.

2. Heterochromia irides

One animal with heterochromia irides had no gross or microscopic lesions. However, the eyes had pigment anomalies and hypoplasia of the iris stroma. Iris pigmentation was reduced in all three layers and the stroma showed clumping and irregular distribution of pigment (Figure 51). The remaining eye structures such as the sclera, choroid and retina had reduced amounts of pigment.

3. Histology of Hair Samples

Comparative histological studies were done on hair samples from the albino cow, her albino son, cows affected with heterochromia irides (brown and white areas), and four normal herd cows (brown and white areas). No pigment was found in hair samples from the albino bull calf except for the brown spot where the amount and distribution of pigment was normal. However, the albino cow had slight traces of pigment granules in some cross sections of the medulla of the hair.

Hair samples from the brown areas in heterochromic and normal cows were undistinguishable. The white areas of the heterochromic cases, however, consistently seemed to have fewer pigment granules in the hair medulla.

C. Herd History

The herd was founded about 50 years ago with a few Hereford cows owned by the mother of the present owner. Until very recently when the herd was expanded by purchase of females, not included in this study, nearly all females in the herd were matrilineal descendants of one of that original few (Plate 1). Two or three herd sires are maintained and usually purchased after progeny test in other herds. Progeny of eight unrelated herd sires were examined. Five of the bulls sired daughters with heterochromic irises; one of these also sired the albino cow. A sixth bull sired the albino son of the albino cow. Two herd bulls, one with one daughter and the other with eight, had no affected progeny recorded. The number and kinds of progeny from various matings are shown in Tables 4 and 5 .

D. Blood Typing and Blood Smears.

Parentage information was consistent with blood typing findings on 29 of 31 animals. For two animals, one case of heterochromia irides and one normal, the dam's blood type was not consistent.

The blood smears were checked for the presence of abnormal granulations in leucocytes. These anomalous structures were reported to occur in the Chediak-Higashi syndrome, partial albinism being part of the syndrome (37). Neither the albino animals nor the cows affected with heterochromia irides had any abnormal granulations in the peripheral blood leucocytes.

DISCUSSION

It is evident that the white, glass-eyed cattle in Herd 1 are albinotic, for most possess no visible color in either their skin or hair. It is equally evident that they are not true albinos in a strict sense for all have blue irises, a characteristic which, from histological evidence from a single eye of seemingly identical appearance, signals at least a partially pigmented retina. Since the pigment cells of the retina are derived from a different line of ectodermal cells than the pigment cells of the other iris layers, skin, and hair, one might suppose that the basic hereditary defect involved only the latter melanocyte system. However, the absence of pigmentation in the posterior part of the retina suggests that the epidermal melanocytes also may be affected. Furthermore, the brown hair spots and pied irises of some animals indicate the presence of functional melanocytes in restricted areas.

Although histological examination of the hair from one white, glass-eyed heifer revealed no pigment in any part of the hair or skin sampled, examination of samples from other animals, particularly the spotted ones, may reveal pigment. A histological investigation of more material remains to be done. Even this may not be a critical test, for Washburn and his coworkers (56) found melanin not only in white hairs from colored Herefords, Holsteins, and Guernseys but also in albino white hairs.

With respect to inheritance, both the white coat and glass-eyes seem to be controlled by a major gene at one locus. If the owner's statements concerning Bulls X and Y are accurate, the gene is dominant. The variable expressivity of the condition evidenced in pigmented hair spots as well as by irises of different blues and greys and spotting, may be a dosage effect, or may be the result of modifiers of one sort or another. On the other hand, if the owner's state-

ments were not accurate, the condition might well have been transmitted as a recessive. It would not be difficult to start with a single albino female in 1951 in a herd of 90 and 14 years later have a herd containing 60 white and 30 colored animals. In Detlefsen's report (11), the herd owner's information led him to suppose that albinism was inherited as a dominant. However, all other reported cases seemed recessive.

The dominance of this gene, however, was confirmed with breeding trials. The white glass-eyed bull purchased sired two progeny with normal coat and eye color and two albinos. The owner had stated that the bull was heterozygous although he had no written record of the ancestors.

The underlying defect in this condition is unknown but might be evaluated by different methods, for example, by tissue culture of skin to test for tyrosinose uptake. This also would answer partly the question whether this mutant gene is located at the C locus. There are number of other loci which are known to cause albinotic dilution of coat color in laboratory animals, domestic animals, and skin in man. They are variably designated and the basic defect of those is not felt to be an enzyme deficiency but rather a defect of the cellular components or failure of immigration or death of melanocytes.

There is not much clinical difference between these animals and the other reported cases of albinism (see Table 2). The main difference lies in the fact that all other cases of albinism with sufficient evidence for genetic analyses have been recessive. Hence, this finding adds a new component to bovine albinism. In man, on the contrary, family pedigrees with dominant and recessive type of inheritance of incomplete general albinism have been reported (15).

The pigmentation anomalies of the two albinos in Herd 2 are those of incomplete general albinism. Certain features reported for other albinos (see Table 2) namely, white coat color, pinkish skin, unpigmented muzzle and clear

yellowy claws also were observed in these animals. The iris colors of the two animals, however, were distinctly different from those described by other workers (see Table 2). The flecked iris of the albino cow and the piebald iris of the albino steer have never been described for the bovine. Likewise, a ghost pattern was absent in the cow but its development may have been prevented in the steer by removal of the gonads. Besides these clinical features, the histological findings from sections of the iris of the steer clearly demonstrate that this color dilution in the iris is due not to the absence of pigmentation but to a clumping of the melanin granules. Furthermore, some consideration has to be given to the presence of the pituitary cyst which has not yet been reported in man or other animals to be associated with color deficiencies. This cyst may be a coincidental finding; however, it may just as well be associated with the pigmentation defect.

The two albinos in Herd 2 differed from those in Herd 1 in clinical and histological features. The appearance of the coat, hair, claws and skin is similar. The eyes, however, show differences. In Herd 1 there is a unique whitish-blue iris present. The few spotted irises seen had much larger areas of pigment than those found in the cow of Herd 2 . The preliminary histological findings on one enucleated eye show that the pigment anomaly in Herd 1 probably is not due to a clumping effect but rather due to a general reduction of iris pigmentation. Furthermore, isolated ocular pigment disorders have never been recorded or seen in colored animals in Herd 1 .

However, additional investigations might prove that selection in Herd 1 accounts for the differences. A breeding test from animals of the two herds would settle easily the question of the allelism of the genes.

The ocular pigmentation anomalies found in Herd 2 in cattle with colored coats apparently have not been reported previously in cattle (20, 59).

Preliminary histological examinations revealed that iris leaf was hypoplastic and had lesser and clumped pigment. This and the lesser pigmentation evidenced in the fundus on opthalmoscopic investigation and the lesser pigmentation of the iris seem to be the underlying causes of the anomaly. The ocular anomaly was more pronounced in the two albinos than in the cows with colored coats; nevertheless, the condition seems likely to have the same cause in both kinds of animals, even though the albino cow's son irises exhibit a unique variegation in color. With respect to the inheritance of the two conditions, they may be considered as two genetic entities or as a single entity. Consider first that the two conditions are separate entities (see Plate 1).

With respect to albinism, a recessive mode of inheritance would fit the facts though necessitating certain relatively impossible events. The albino cow's two mutant genes might have arisen either as two new mutants, or as one new mutant and a copy of a parental mutant, or as copies of two parental mutants. The parental mutants could have arisen in the same fashion as could the mutants in any ancestral generation. The probabilities associated with the various possibilities can only be estimated crudely but the differences in their magnitude are rather large.

Since albinos are undesirable in most herds, presumably nearly all are eliminated. Thus, the frequency of the recessive albino gene in a large random mating population ought to be near an equilibrium value of $\mu^{1/2}$, where μ is the forward mutation rate and back mutation is ignored. In such a population the probability of an animal having two new mutant genes is near but less than μ^2. The probability of having one new and one old is in the order of $2\mu^{3/2}$ and the probability of two old mutants is in the order of μ. Hence, the most probable origin of the albino cow's mutant genes seems to be as copies of parental mutants. Copies of the paternal mutant could be possessed by a number

of mates of bull I , depending on the source of the gene. Under these circumstances additional albinos might have been expected among I's progeny.

If, on the one hand, the albino cow's maternal gene for albinism was a copy of that possessed by the maternal grandsire D, other copies of the same gene ought to have been possessed by half the daughters of the bull., i.e., half the females of generation line VII ought to have been heterozygous. Four daughters (VII-3,5,6-7) had 6 descendants mated with bull I , the albino's sire. One albino resulted from the six when the expected proportion was about one from sixteen. If, on the other hand, the maternal gene was a copy of one of the maternal granddam's other copies of the same gene could have been possessed by at most only a very few other animals. Thus, the expected proportion of albinos among the progeny of it would have been much smaller than expected if the maternal gene has been from the maternal grandsire.

Hence, there is nothing in the information from close relatives to refute a recessive hypothesis. Furthermore, the owner thought there was no close relationship between the parents of the albinos.

The albino cow had 4 progeny by three different males; one was albino. It is that calf that stretches the credibility of the simple recessive hypothesis. The rare probabilities involved in the occurrence of the albino cow are accepted easily, but the likelihood of the owner subsequently choosing yet another heterozygous male is so remote as to cast doubt on the hypothesis.

The simplest alternative explanation is that the albino cow received either a newly mutant dominant gene from her dam or sire, or a copy of an old incompletely penetrant dominant mutant gene from her dam. That the gene was not a copy of an old incompletely penetrant mutant possessed by her sire seems quite probable. For the albino to be the only one of more than 40 paternal sisters to have received such a gene from her sire requires either an exceedingly rare sampling

event or a gene of such low penetrance that a copy of it would scarcely be expected to evidence itself later in one of only 4 progeny of the albino cow.

The independent inheritance of heterochromic irises may be a dominant gene. Since the condition has not been described previously, presumably it is rare in the breed. Hence, all the mutant genes ought to be copies of a single ancestral mutant and the animals which possess the genes, close relatives. To the best of the owner's knowledge, the only foundation animals that might have been related were the foundation cow, Brat (I-2), and the bulls A, G, and the sire of cows III-2 and III-3 .

It is evident from Plate 1 that the gene may have been introduced into the herd in several different ways. Every explanation involving the related foundation animals requires that the cow Brat had the gene. It is important to remember that the owner and others working the herd had noted only recently a few of the 26 cases. Thus, the condition may be overlooked easily and may have been present in the herd for many years.

The simplest hypothesis is that the gene was transmitted only matrilineally, through Brat and her descendants. On that basis the probabilities of each living descendant in the genealogy having heterochromic irises may be calculated.

Twelve cows were expected to have heterochromic irises whereas 23 did, a highly improbable discrepancy ($X^2 = 10.20$, $P < .005$). Another introduction would be through cow Brat and bull G ; about 16 heterochromic iris cows would be expected but 25 were observed, a highly improbable discrepancy ($X^2 = 7.76$; $.01 > P > 0.05$). A third method of introduction would be through Brat, bull G and the sire of VII-2 and III-3 . The expected number was 19 and 23 were observed, a statistically insignificant discrepancy ($X^2 = 1.84$; $P > .05$). Other methods of introduction involving bull A yield similar suitable expectations.

Finally a simple recessive inheritance of heterochromic irises seems easily ruled out by the improbability of choosing from five other herds at least 5 herd sires heterozygous for a relatively rare gene to be used in a herd where the gene must have been at rather high frequencies already.

Consider next the possibility that the two conditions are regulated by the same locus. The most obvious hypothesis is that heterochromia irides represents heterozygosity and albinism, homozygosity. The albinos cow's albino son by a normal eyed bull disproves this or requires a more complex hypothesis. Another hypothesis would be to suppose that the gene has a wide range of expression extending from heterochromia irides to complete albinism. Since something more than 40 animals with heterochromia irides likely were included in the entire genealogy, it seems improbable that the only two extreme cases of expression should have occurred in mother and son.

For want of sufficient evidence to resolve these more complex hypothesis, it seems best to suppose the inheritance of the two conditions as independant dominants.

CONCLUSIONS

Investigations of albino animals in two Kansas herds have been reported. A western Kansas herd of about 90 animals, including 60 white albinotic animals, and 30 colored animals, descended primarily from grade Hereford cows and a few Holsteins and Guernseys. The whites descended from a single grade albinotic Hereford female. The mode of inheritance was demonstrated by breeding trials to be dominant.

Most of the white cattle had completely white hair coats and skins but a few had small brown spots on the shoulder or the hip. The eyes were glass-eyes;

most irises hsowed only a very faint blueness. A few, however, showed irregular splotches of white, blue, and brown. Histological examination of one eye showed pigment only in the posterior layer of the iris and the anterior portions of the retina; the tapetum lucidum was void of pigment and appeared orange on opthalmoscopic investigation. In daylight, the pupils appeared brown; under reduced light, muddy pink.

The occurrence of a thus far undescribed albinism in another Kansas Hereford herd is also reported. Features of this condition were coat color dilution and heterochromia irides. In this herd, the albino cow had grey-blue irises with tiny spots. Her son had piebald irises.

Furthermore, in this same herd, 25 animals of normal Hereford coat color and pattern had heterochromia irides. Neither condition has been described previously in cattle. Both albinism and heterochromia irides seem to be dominants.

The histological features of these conditions are absence of pigment in the skin and a disturbed pigmentation pattern of the iris. In both the albino and heterochromic iris cattle, there was an unusual clumping of melanin granules.

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Table 1

Differential Diagnosis of Different Forms of

	Complete General Albinism
Ocular Symptoms	
Iris	Pink or pale blue; hypoplasia
Fundus	No pigments
Signs in heterozygotes	Diaphanous iris
Correlations	Myopia; astigmatism lacunae of iris
General Symptoms	
Skin	White
Hair	White or straw-colored
Correlations	Psychic abnormalities; hypogenitalism
Heredity	Autosomal recessive

* Cited from: J. Francois, "Heredity and Ophthal-
St. Louis, 1961.

Albinism in Humans

Incomplete General Albinism	Ocular Albinism	Partial Albinism
Yellowish-green or blue	Hypopigmented or normal	Generally normal
Albinistic, but sometimes more or less pigmented	Albinistic, but sometimes a little pigmented	Normal
Diaphanous iris	Diaphnous iris; fundus characteristic	
Myopia	Myopia; astigmatism, lacunae of iris	Lateral displacement of internal canthi; hyperplasia of eyebrows; heterochromia
More or less pigmented	More or less pigmented; sometimes normal	Restricted depigmented areas
Blond	More or less pigmented; sometimes normal	White forelock
	Psychic abnormalities	Deaf and dumb; hyperplasia of base of nose
Autosomal recessive or dominant	Sex-linked recessive	Dominant

mology." The C. V. Mosby Co.,

Table 2

Recorded Descriptions of Bovine Albinism

Reference	Year	Breed	Mode of Transmission	Number of Albinos observed	Iris Color	Pupil Color	Hair	Skin
(11)	1919	Holstein	recessive	20	pink	pink	white	dark spots on ears and muzzle
(4)	1934	Brown Swiss	recessive	22	white	pink	white	pinkish
(8)	1934	Holstein	recessive	5	gray	pink	white	"ghost pattern"
(22)	1937	Holstein	recessive	3	blue-gray	pink	white	pink
(24)	1926	Unknown	recessive	1	light blue	pink	white	white
(39)	1944	Holstein	recessive	43	----------	----	white	"ghost pattern"
(35)	1959	Herefords	recessive	3	----------	----	white	dark spots on legs
(46)	1959	Murbodner Breed	recessive	1	pink	pink	white	pink
(57)	1964	Brown Swiss	recessive	3	pink	pink	white	white

TABLE 3 Nature of iris in cattle with heterochromia irides

Cow No.	Age	Sire	Iris Discoloration Right	Iris Discoloration Left	Iris Pigment Reduction Degree	Iris Pigment Reduction Expression*
VII - 7	12	E	4 to 7	5 to 7	III	d
VII - 8	11	E	5 to 7	4 to 7	III	d
IX - 5	10	F	slightly affected		I	c
IX - 6	10	F	3 to 9	6	II	d
IX - 7	10	F	slightly affected		I	c
IX - 8	11	F	moderately affected		II	c
X - 22	8	G	3 to 9	3 to 9	IV	c
X - 8	6	G	5 to 7	6	II	d
X - 12	8	G	3 to 9	3 to 9	IV	c
X - 15	8	G	5 to 7	5 to 7	III	c
X - 17	8	G	5 to 7	5 to 8	III	d
X - 18	8	G	6 to 7	normal	I	u
X - 19	8	G	moderately affected		II	c
X - 20	6	G	0 to 12	4 to 9	IV	d
X - 21	8	G	0 to 12	0 to 12	V	c
XI - 5	6	H				
XI - 6	6	H	4 to 6	6	II	d
XI - 9	6	H	5 to 7	5 to 7	III	c
XI - 10	5	H	normal	6 to 7	II	u
XII - 2	4	I	5 to 7	slight	III	d
XII - 8	4	I	5 to 6	5 to 7	III	d
XII - 14	5	I	moderately affected		II	c
XII - 30	3	I	6	5 to 8	III	d
XII - 40	5	I	slightly affected		I	c
XII - 41	4	I	5 to 7	5 to 7	III	c

*Expression: c=concordant
d=discordant
u=unilateral

Table 4 . Pigmentation of Progeny from Various Matings

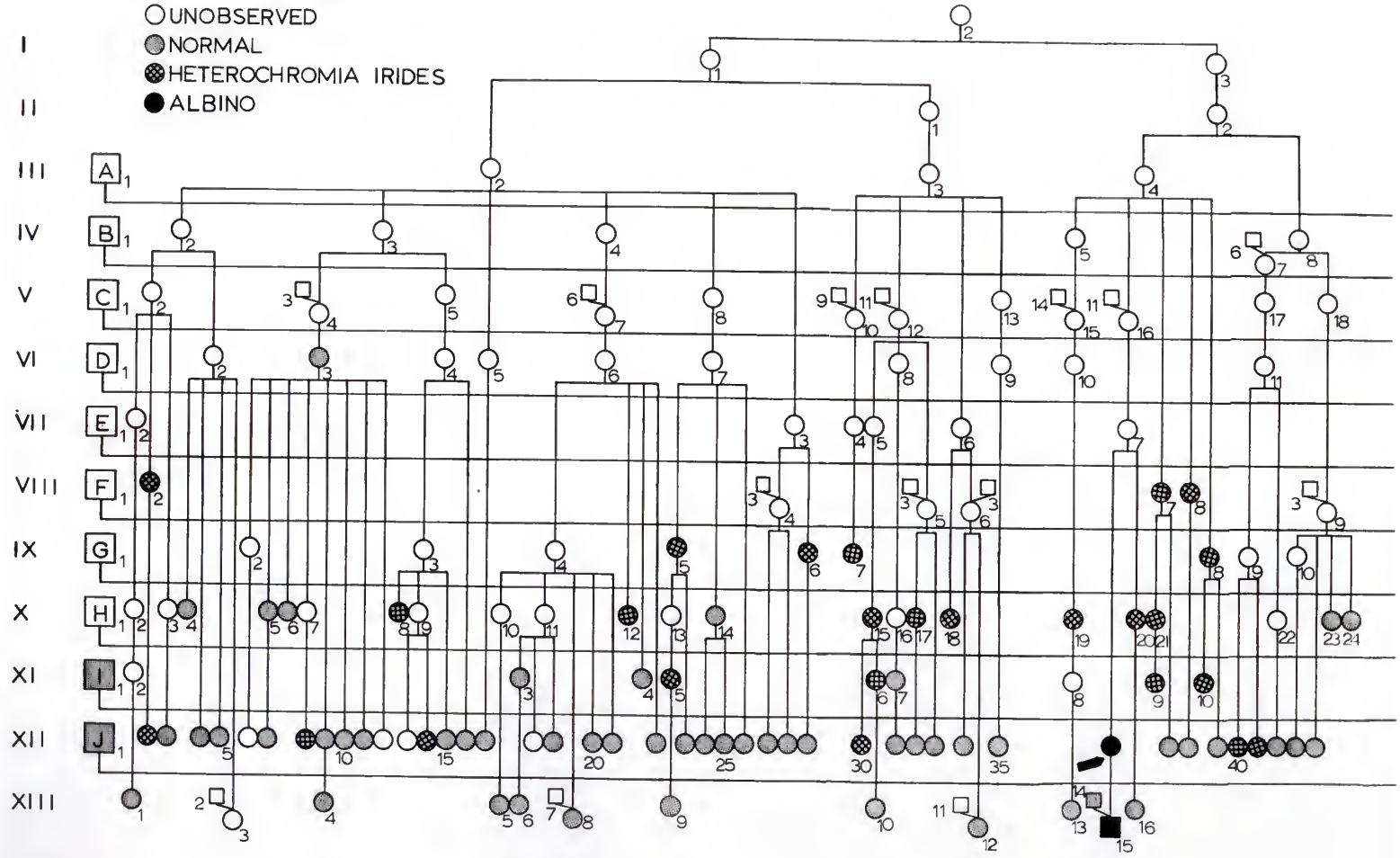
Parental Mating Type		Progeny Phenotypes			
		Normal	Heterochromia Irides	Albinos	Total
Normal	Normal Heterochromia	9	0	0	9
Normal	Irides	9	2	0	11
Normal	Unobserved	22	4	1	27
Unobserved	Normal	2	0	0	2
Unobserved	Heterochromia Irides	0	4	0	4
Normal	Albinos	0	0	1	1
Unobserved	Unobserved	12	15	0	27
Total		54	25	2	81

Table 5 . Pigmentation Anomalies of Progeny of Eight Sires

Sire	Progeny No.	Av. Age	Normal	Heterochromic Iris	Albino
C	1	15	1 (100%)		
E	2	11.5		2 (100%)	
F	4	10.0		4 (100%)	
G	15	7.4	6 (40%)	9 (60%)	
H	6	5.7	2 (33%)	4 (67%)	
I	39	5.4	32 (82%)	6 (15%)	1 (3%)
J	8	3.3	8 (100%)		
XIII-14	1	1.0			1 (100%)
	76	5.4	49 (64%)	25 (33%)	2 (3%)

Two cows (XIII-8 and XIII-12) are by unknown sires

Three normal bulls (I, J, and XIII-14)= 76 + 2 + 3 = 81


KEY:
FEMALE
MALE
UNOBSERVED
NORMAL
HETEROCHROMIA IRIDES
ALBINO
I
II
III
IV
V
VI
VII
VIII
IX
X
XI
XII
XIII
A
B
C
D
E
F
G
H
I
J

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FIGURES

Figure 1 . Bull X . Note pronounced photophobia even on a cloudy day.

Figure 2 . Bull X . Note the appearance of the eye.

Figure 3 . Albino cow; her dam, a Guernsey; her sire, bull X .

Figure 4 . Head of Guernsey - albino crossbred in Figure 3 . Note appearance of iris.

Figure 5 . Albino calf; dam, albino - Guernsey crossbred in Figure 3 , sire, unknown.

Figure 6 .

Figure 7 .

Figure 6 . Albino - Guernsey crossbred of Figure 4 with calf of Figure 5 .

Figure 7 . Holstein - Hereford crossbred cow, unrelated to albino animals, and her bull calf, sired by X . Note calf is photophobiac.

Figure 8 .

Figure 8 . Left eye of an albino calf. The eyelids, conjunctiva and nictitating membrane are unpigmented. The iris is white in the outer peripheral parts, and pale blue in the center. Note the increased lacrimal flow due to photophobia. The picture was taken with flash bulb in daylight.

Figure 9 . An albino eye under reduced light.

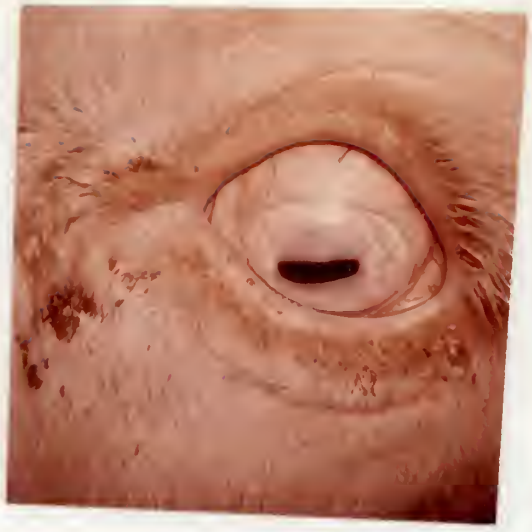

Figure 10 .

Figure 11 .

Figure 10 . Albino eye. Note appearance of iris and the clear visibility of iridial and conjunctival vessels due to the absence of pigment. Picture was taken with flash during daylight.

Figure 11 . Albino eye under reduced artificial light. Note the albinotic pupillar reflection.

Figure 12 . Frozen half of albino eye, demonstrating absence of pigmentation in the fundus. The posterior layer of the iris is pigmented. External appearance of this iris is shown in Figure 10 .

Figure 13 . The albinotic fundus.

Figure 12 .

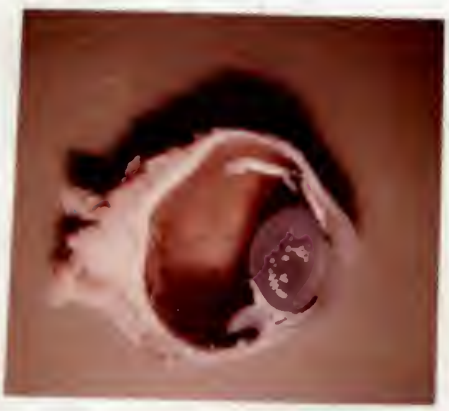

Figure 13 .

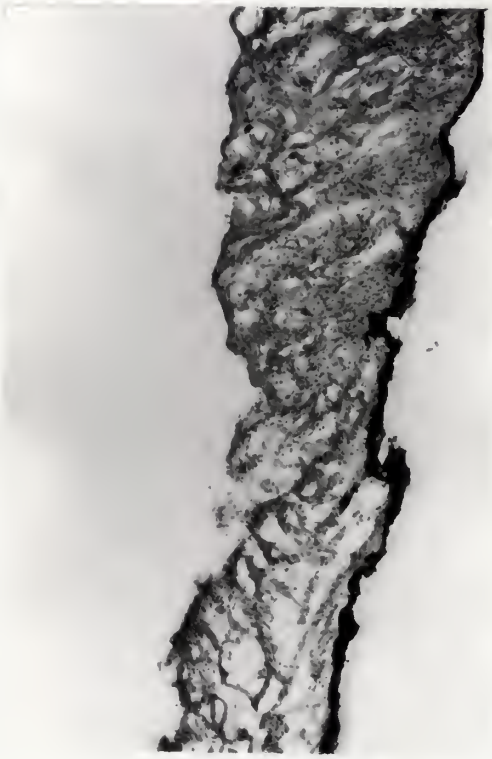

Figure 14 . Microscopic section of an albino iris. External and gross appearance are shown in Figures 10, 12, and 13 . Note absence of pigmentation in iris stroma and anterior layer. Note pigmentation in the posterior layer. Hematoxylin and eosin, frozen section 50 x .

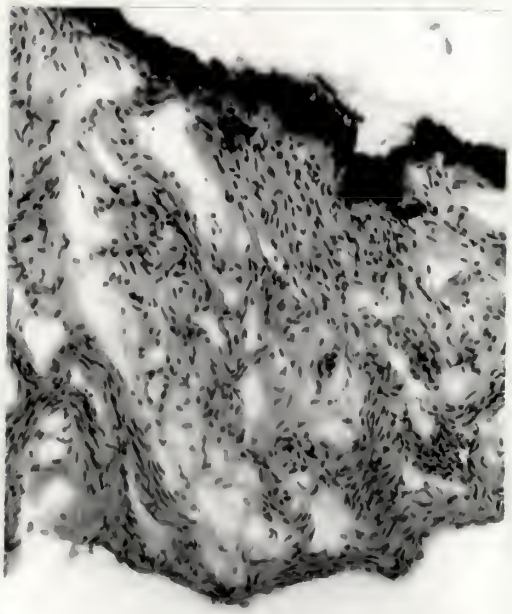

Figure 15 . This section of Figure 14 magnified 125 x .

Figure 16 . Fundus showing absence of pigment. Hematoxylin and eosin, 125 x .

Figure 17 . Albino heifer calf with heterochromia irides. Parents were albino bull and Holstein cow.

Figure 18 . Left eye of albino calf shown in Figure 17 .

Figure 19 . Right eye of albino calf shown in Figure 17 .

Figure 20 . Albino cow. Note extreme photophobia although picture was taken in late afternoon sun.

Figure 21 . Albino bull calf, son of albino cow shown in Figure 20 . Note dark brown spot on right shoulder.

Figure 20 .

Figure 21 .

Figure 22 . Right eye of albino cow shown in Figure 20 . Note absence of pigment and also color of iris. Photophobia is expressed in extreme narrowing of pupil. Picture was taken in daylight using flash bulb.

Figure 23 . Left eye of albino. Note the slight difference in iris color compared to that of the right eye.

Figure 22 .

Figure 23 .

Figure 24 . Right eye of albino cow shown in Figure 20 . Different colors of the iris are expressed as different shades of grey.

Figure 25 .

Figure 26 .

Figure 25 . Right eye of albino bull calf shown in Figure 21 . Note absence of pigment in eyelids, conjunctiva, nictitating membrane. Photophobia is expressed in increased lacrimal flow and extreme narrowing of pupil.

Figure 26 . Left eye of bull calf shown in Figure 21 . Note difference of iris color and color pattern in the two eyes.

Figure 27 . Muzzle of albino bull calf shown in Figure 21 . Note pinkish appearance.

Figure 28 . Albino bull calf shown in Figure 21 . Note pinkish appearance of muzzle, lips, gingiva and palate.

Figure 27 .

Figure 28 .

Figure 29 . Right lateral section of eye of albino bull. Note the presence of pigment in parts of the retina. The tapetum luicidum has been replaced by a pinkish white area.

Figure 30 . Pituitary of albino bull calf. Note the rather large cystic residual hypophyseal lumen filled with a yellowy watery fluid.

Figure 29 .

Figure 30 .

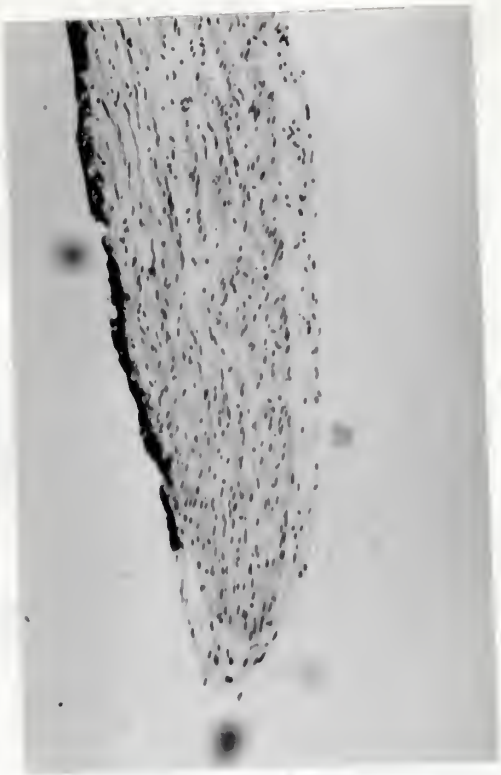

Figure 31 . Medial section of iris, upper part; the color in this area was pale blue. Note absence of pigment in anterior layer and stroma of the iris whereas posterior part is slightly pigmented. Hematoxylin and eosin, 125 x .

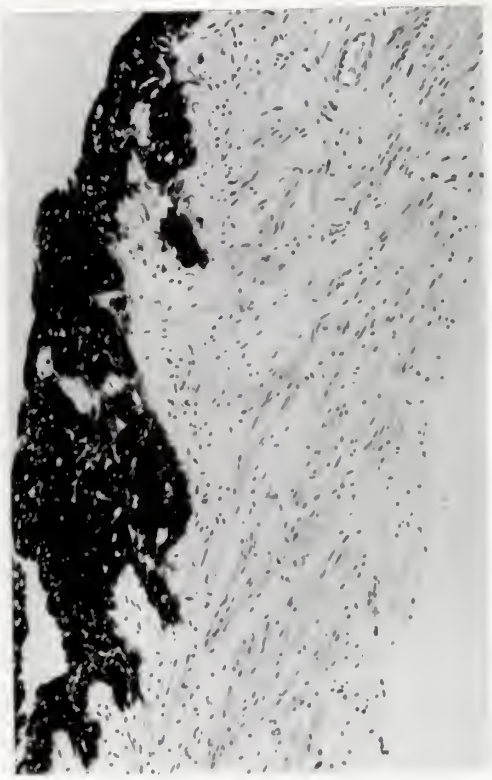

Figure 32 . Medial section of iris leaf. Gross appearance of iris in this area was a glistening white. Note hyperpigmentation of posterior part of the iris whereas mesodermal layer and anterior part are devoid of pigment. Hematoxylin and eosin, 125 x .

Figure 33 . Right eye, central section; the iris color was grey. Note hyperpigmentation of posterior layer of the iris. Mesodermal and anterior layer are slightly pigmented. Hematoxylin and eosin, 125 x .

Figure 34 . Left eye; medial section of the iris leaf, upper part. The iris color was a mottled grey. Note the absence of pigment in iris stroma. The posterior layer is slightly pigmented. The anterior portions of the stroma reveal abnormal, large clumps of melanin granules. Hematoxylin and eosin, 125 x .

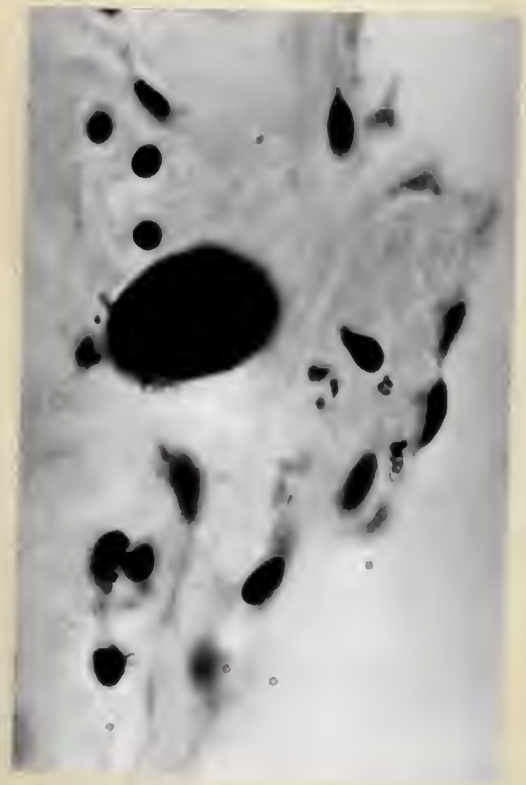

Figure 35 . Left eye, upper part of iris leaf, medial section. Abnormal clumping of melanin granules in anterior portion of iris of an albino calf. Hematoxylin and eosin oil immersion, 1 000 x .

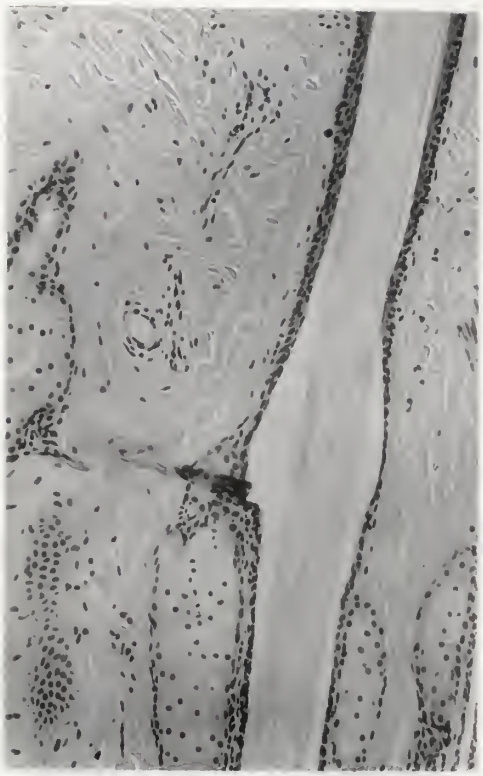

Figure 36 . Section of albino skin. Note absence of pigment particularly in longitudinal section of hair. Hematoxylin and eosin, 125 x .

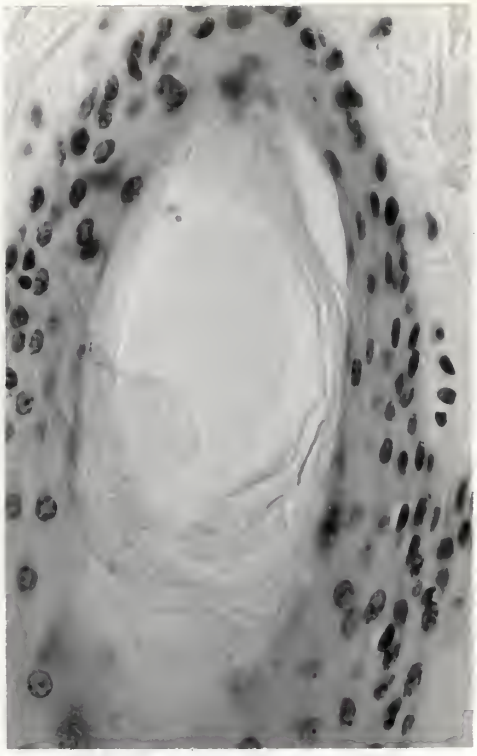

Figure 37 . Albino skin; cross section of hair bulb. Hematoxylin and eosin, 500 x .

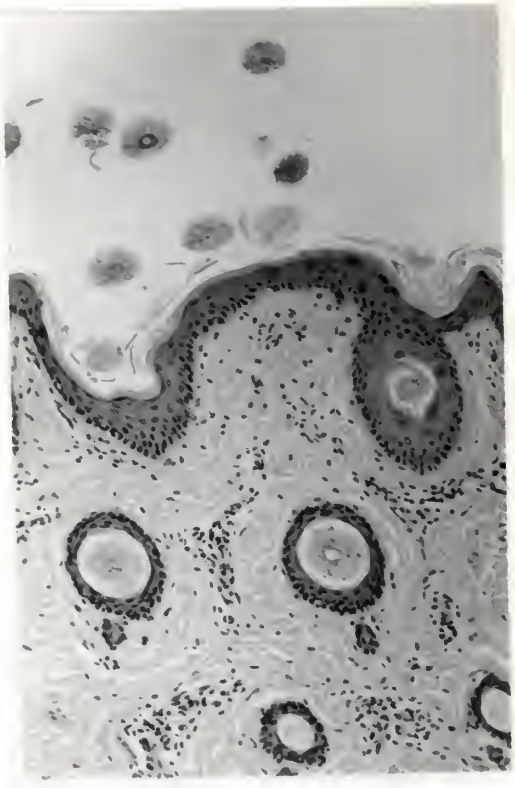

Figure 39 . Section of the skin taken from the small brown spot on right shoulder of an albino calf. Note pigment in hair shaft. Hematoxylin and eosin, 125 x .

Figure 41 . Section of muzzle of albino. Hematoxylin and eosin, 125 x .

Figure 42 . Left eye cow XII - 41 . Heterochromia irides.

Figure 43 . Right eye cow XII - 41 . Heterochromia irides.

Figure 44 . Heterochromia irides, left eye cow VII - 7 .

Figure 45 . Heterochromia irides, right eye cow VII - 7 .

Figure 46 . Heterochromia irides, left eye cow X - 12 .

Figure 47 . Heterochromia irides, right eye cow X - 12 .

Figure 48 . Heterochromia irides, cow X - 15 .

Figure 49 . Heterochromia irides, cow X - 15 .

Figure 50 . Heterochromia irides.

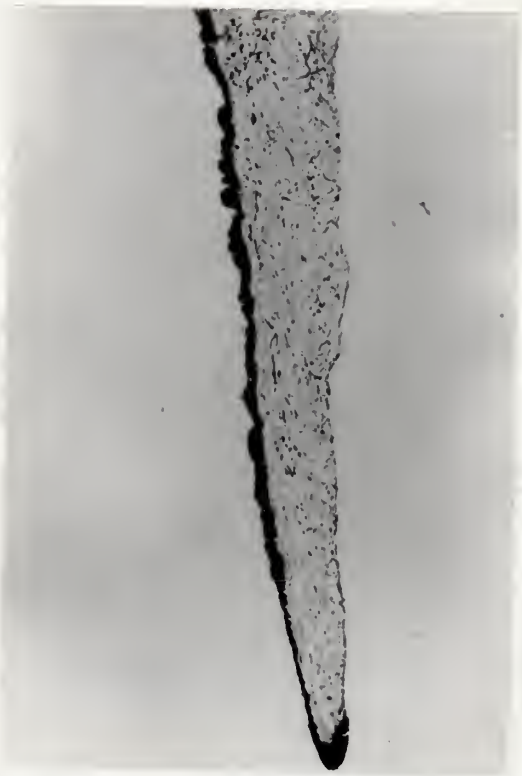

Figure 51 . Heterochromia irides. Note hypoplasia of iris stroma and reduced pigmentation in all 3 iris layers. Hematoxylin and eosin, 50 x .

ALBINISM AND HETEROCHROMIA IRIDES IN THE HEREFORD

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Diploma Justus Liebig-University 1960

Doktor der Veterinaermedizin Justus Liebig-University 1963

AN ABSTRACT OF A MASTER'S THESIS

submitted in partial fulfillment of the

requirements for the degree

MASTER OF SCIENCE

IN GENETICS

KANSAS STATE UNIVERSITY

Manhattan, Kansas

1967

Although albinism in the bovine species has been reported on a number of occasions, there are many anatomic, physiologic and genetic aspects which are not understood. Investigations in two herds containing albinos are reported here.

The first herd was observed in western Kansas, a second herd, in southwestern Kansas. The latter contained also normal colored Herefords with heterochromia iridcs. Both herds were visited on a number of occasions. Breeding histories were obtained and clinical inspections were done in both herds.

The albino animals (about 60) in Herd 1 had, with a few exceptions, the following features: every animal was pure white, had pinkish skin, clear yellowy claws. The eyes had a unique iris color: a pale blue center and an outer peripheral white zone. Skin and hair biopsies of one animal had no pigment. One enucleated eye, however, revealed presence of pigment in the posterior iris layer and the retina. All other ocular structures were void of pigment.

The breeding history suggested a dominant gene for this type of albinism; however, the owner did not keep adequate breeding records. One albino bull, reportedly heterozygous, was purchased and four test matings done. The mates were 1 Holstein, 2 Jersey cows, and a Hereford dwarf. The Holstein cow and one Jersey cow delivered typical albinos; the other two were normal. Hence, this dominant type of albinism is new finding for the bovine.

In the second herd, two albinos, a mother and her son, were observed. Both had the typical albino skin and hair. However, the irises of the cow were pale blue with fine spotting. Her son had so-called piebald irises. Neither condition has been described in cattle. The albino steer was available for detailed anatomical and histological studies. The only gross finding was a large residual hypophyseal lumen. The histological studies of eye sections revealed disturbed pigmentation pattern in the iris, mainly a large clumping of melanin

granules.

In addition to the two albinos, in this herd 25 animals of normal Hereford color were observed with heterochromia irides. The ophthalmoscopic investigation signaled a reduced ocular pigmentation. Again, the iris was mainly affected, being hypoplastic and having the same disturbance in distribution and the same clumping of pigment, although to a lesser degree.

On the basis of the available data, the inheritance of heterochromia irides was established as dominant. The inheritance of albinism in this herd also appears to be dominant.

The findings here are compared to recorded cases of bovine albinism. All bovine cases reported have been recessive. In addition, isolated ocular pigmentary disorders have not been described previously in cattle. The occurrence of albinism and related defects in other domestic animals also is discussed.